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| **Division** | : | Worldwide Development |
| **Information Type** | : | Reporting and Analysis Plan (RAP) |

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|---|---|---|
| **Title** | : | Reporting and Analysis Plan for A Phase 1, Multicompartmental Pharmacokinetic Study of Cabotegravir Long-acting in Healthy Adult Volunteers |
| **Compound Number** | : | GSK1265744 |
| **Effective Date** | : | 14-AUG-2019 |

**Description:**

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 201767
- This RAP is intended to describe the safety, pharmacokinetics, and tolerability analyses required for the study
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

**RAP Authors:**

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# 1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

| **Revision Chronology:** | | |
|---|---|---|
| GSK Document No.: 2014N213747_00 | 2015-MAY-04 | Original |
| GSK Document No.: 2014N213747_01 | 2015-NOV-10 | Amendment No. 1: includes additional exclusion criteria for subjects with history of seizure disorder |
| GSK Document No.: 2014N213747_02 | 2016-MAR-30 | Amendment No. 2: updated the CAB LA IM dose from 800 mg (split 2 x 400 mg injections) to a single 600 mg IM dose. In addition, tissue collection on Day 3 (48h post-injection) was changed from optional assessments to required assessments per protocol and removed vaginal tissue collection on Day 8, Week 4 and 12. Lastly, MRI assessments were changed from optional assessments to required, updated dose rationale, and miscellaneous changes for clarification. |
| GSK Document No.: 2014N213747_03 | 2017-Aug-14 | Amendment No. 3: updated the wash-out period between oral and LA dosing to accommodate visit scheduling and removed the needle length specification for intramuscular injection in Section 6.1.3. |

# 2. SUMMARY OF KEY PROTOCOL INFORMATION

## 2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol dated 04-MAY-2015, protocol amendment 1 dated 10-NOV-2015, protocol amendment 2 dated 30-MAR-2016 and protocol amendment 3 dated 14-AUG-2017.

## 2.2. Study Objective(s) and Endpoint(s)

| Objectives | Endpoints |
|---|---|
| **Primary Objectives** | **Primary Endpoints** |
| • To determine the pharmacokinetic concentrations of CAB following LA administration in blood plasma and in vaginal tissue (VT), cervical tissue (CT), and cervicovaginal fluid (CVF) in healthy women and in rectal tissue (RT) and rectal fluid (RF) in healthy men and women (as data permit) following a single 600 mg intramuscular dose. | • Concentrations observed at Day 3 (C48h), Day 8 (Cd8), Week 4 (CWk4), Week 8 (CWk8), and Week 12 (CWk12) in blood plasma and in CT, and CVF in women, and in RT and RF in men and women (as data permit) following a single CAB 600 mg intramuscular dose.<br>• VT concentrations observed at Day 3 (C48h), and Week 8 (CWk8), in women following a single CAB 600 mg intramuscular dose. |
| **Secondary Objectives** | **Secondary Endpoints** |
| • To compare the pharmacokinetic concentrations following a single intramuscular dose of CAB LA 600 mg in VT, CT, and CVF relative to blood plasma and CVF in healthy women, and in RT and RF relative to blood plasma and RF in healthy men and women (as data permit). | • Concentration ratios including VT:blood plasma, CT:blood plasma, CVF:blood plasma, CT:CVF, VT:CVF in women, and RT:blood plasma, RF:blood plasma and RT:RF in men and women (as data permit) at matched timepoints evaluated. |
| • To describe the pharmacokinetic profile of CAB LA in blood plasma and CT, CVF, in healthy women and in RT and RF in healthy men and women (as data permit) following a single 600 mg intramuscular dose. | • Maximum observed concentration (Cmax) and time of maximum observed concentration (tmax) in blood plasma and in CT, CVF, RT, RF matrices.<br>• Area under the concentration time curve from time zero to last quantifiable time point (AUC(0-last)), area under the concentration time curve from time zero to infinity (AUC(0-∞)), area under the concentration time curve from time zero to Week 4 (AUC(0-Wk4)), area under the concentration time curve from time zero to Week 8 (AUC(0-Wk8)) area under the concentration time curve from time zero to Week 12 (AUC(0-Wk12)) and apparent terminal phase half-life (t½) in blood plasma, CT, CVF, RT, RF, as data permit.<br>• Tissue:blood plasma and fluid:blood plasma ratio of AUCs of intervals specified above. |
| • To determine the trough concentration achieved following repeat administration of oral CAB 30 mg once daily to steady | • CAB concentration ($C_{24}$) following oral administration in VT, CT, CVF, RT, RF and blood plasma. |

| Objectives | Endpoints |
|---|---|
| state in blood plasma and VT, CT, and CVF in healthy women and in RT and RF in healthy men and women (as data permit). | |
| • To assess the safety and tolerability of CAB following repeat oral doses and single dose intramuscular administration in healthy subjects. | • Safety and tolerability parameters, including adverse events, clinical laboratory tests, and vital signs assessments. |
| **Exploratory Objectives** | **Exploratory Endpoints** |
| • To assess evolution of the injection depot localization following a single CAB 600 mg intramuscular dose. | • Volumetric and T1, T2 assessment of depot via non-contrast-enhanced magnetic resonance imaging (MRI) images of the injection site at the time of injection, Day 3 (48 hours) and 1 week post-injection as data permit. |

## 2.3. Study Design

- This will be a Phase 1, open label study in healthy subjects to assess the PKs of CAB LA in the blood plasma and anatomic locations associated with sexual HIV-1 transmission: VT, CT, CVF, RT, and RF.

- The study will consist of a screening period, a 28-day oral lead-in phase using a CAB dose of 30 mg once per day followed by a 14- 42 day washout period, and a single dose of CAB LA 600 mg IM with compartmental PK sampling for up to 12 weeks. Subjects will return for safety assessments and PK sampling of the blood plasma at Week 24 and Week 36 post-injection and undergo a follow-up/withdrawal visit at Week 52 post-injection.

- Approximately 20 healthy subjects from up to two clinic sites will be enrolled such that approximately 16 evaluable subjects (8 males and 8 females) will receive a CAB LA IM dose and complete compartmental PK sampling. Non-contrast-enhanced MRI will be performed in a subset of up to 4 males and 4 females. Evaluable subjects are defined as those who provide at least one primary PK endpoint without major protocol deviations.

- If subjects prematurely discontinue the study, additional replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator. The replacement subject will have same treatment and procedures per protocol as the discontinued subject.

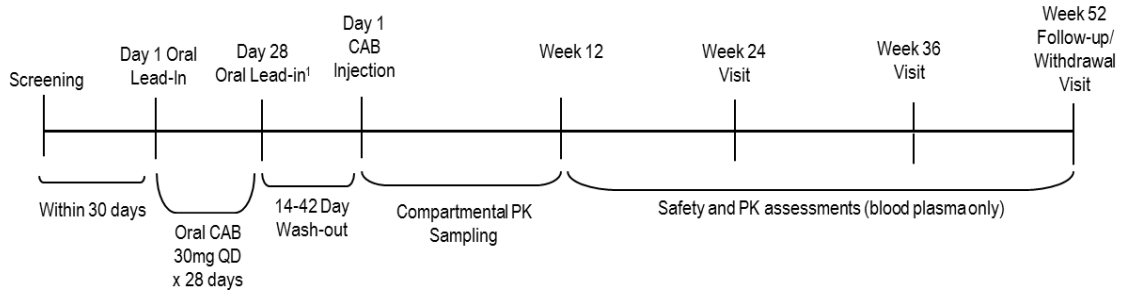
- Each subject will participate in the study for approximately 66 weeks. The study design is defined in Table 1.

**Table 1 Study Design***

| Screening | Oral Lead-in | Washout | CAB Injection and Compartmental PK Sampling | Safety/ Blood Plasma Sampling | Follow-up/ Withdrawal Visit |
|---|---|---|---|---|---|
| Within 30 days of 1st oral CAB dose | Oral CAB 30 mg tablet once daily x 4 weeks | No drug administered 14 – 42 days | Single 600 mg CAB LA IM dose<br><br>Tissue/luminal fluid/blood plasma sampling up to 12 weeks post-injection | Safety assessments and blood plasma PK sampling will occur at 24 and 36 Weeks post-dose | Follow-up assessments to be performed 52 Weeks post-injection |

*Given the cervicovaginal sampling in the protocol, timing and duration of menses should be taken into account when scheduling screening, oral lead-in phase and injection.

**Figure 1 Study Schematic**




1. In addition to compartmental PK sampling following CAB LA injection, subjects will undergo PK sampling of blood plasma and CT/VT/CVF (females) and/or RT/RF after Day 28 of the oral lead-in, on Day 29.

## 2.4. Statistical Hypotheses

The primary objectives of this study are to assess the pharmacokinetics of CAB LA in blood plasma and vaginal, cervical, and rectal tissues and secretions following a single 600mg intramuscular dose. No formal statistical hypotheses are to be tested. Where appropriate, an estimation approach will be taken, and point estimates and confidence intervals will be constructed. There will be no formal comparison.

# 3. PLANNED ANALYSES

## 3.1. Interim Analyses

There will be no formal interim analysis; however preliminary CAB LA PK parameters may be generated and reviewed internally at GSK to assess the current CAB LA batch being used in this study (Protocol Section 6.1.2) relative to historical data.

## 3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

# 4. ANALYSIS POPULATIONS

- **Screened Population**

All subjects who have signed the consent form and enrolled in the study will be included in this population.

- **Safety Population**

All subjects enrolled in the study who have received at least one dose of study drug will be included in the Safety Population. This will be the population for the safety analyses, as well as for presentation and summarization of baseline/demographic characteristics.

- **Pharmacokinetic (PK) Plasma Populations**

| | |
|---|---|
| • **Pharmacokinetic Plasma Concentration Population** | The PK Plasma Concentration Population will include all subjects who undergo plasma and compartmental PK sampling following oral and/or IM injection and have evaluable PK assay results. This population will be used for the concentration listing and individual plotting of the concentration-time data. |
| • **Pharmacokinetic Plasma Parameter Population** | The PK Plasma Parameter Population will include all subjects who undergo plasma and compartmental PK sampling after IM injection and have PK parameters estimated. This population will be used for PK parameter listing. |
| • **Evaluable Pharmacokinetic Plasma Parameter Summary Population** | The PK Plasma Parameter Population will include all subjects who undergo plasma PK sampling after IM injection and have evaluable PK parameters estimated (measurable) and no major protocol deviation (no important protocol deviation). This population will be used for evaluable PK parameters and concentrations' mean/median plots and summary tables. |

- **Tissue and fluid Populations:**

For the tissue or fluid samples, analysis populations will be derived for the following 9 specimens:

| | |
|---|---|
| • **Tissue_fluid PK Concentration Population** | The tissue_fluid PK Concentration Population will include all subjects who undergo VT/CT/CVF/RT/RF sampling following oral and/or IM injection and have at least one evaluable PK assay result in VT/CT/CVF/RT/RF. This population will be used for the individual concentration listing and plot |
| • **Tissue_fluid PK Parameter Population (IM)** | The evaluable tissue_fluid Parameter Population will include all subjects who undergo sampling following IM injection and have at least one evaluable parameter estimated in VT/CT/CVF/RT/RF. This population will be used for the individual parameter listing |
| • **EvaluableTissue_fluid and PK Parameter Population (IM)** | The evaluable PK and tissue_fluid Parameter Population will include all subjects who undergo sampling following IM injection and have both evaluable PK and evaluable tissues_fluid parameters estimated in VT/CT/CVF/RT/RF. This population will be used for the parameter summary and mean/median plots, and ratios calculations. |

## 4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, dosing, conduct of the trial, subject management or subject assessment) will be evaluated and determined by the team and be listed.
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
    - This dataset will be the basis for the listing of protocol deviations.
- A separate listing of all inclusion/exclusion criteria deviations will also be provided if any.

# 5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

## 5.1. Study Treatment & Sub-group Display Descriptors

Data display treatment descriptors with actual treatment dose will be defined as follows:

| RANDALL NG Randomization System | | Data Displays for Reporting | |
|---|---|---|---|
| **Code** | **Description** | **Description** | **Order in TLF** |
| A | Oral CAB 30mg tablet once daily 28 days lead-in | Oral CAB 30mg QD | 1 |
| B | Single 600mg CAB LA IM dose | IM CAB 600mg | 2 |

Footnotes: Oral CAB 30mg=Cabotegravir 30mg QD 28 days lead-in; IM CAB 600mg=Cabotegravir IM 600mg SD.

## 5.2. Baseline Definition

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used.

The following table indicates the baseline day to be used in the analysis for each phase of the study:

| **Parameter** | **Baseline (Predose) Days Collected** | | **Baseline (Predose) Day Used in Analysis** |
|---|---|---|---|
| | **Screening** | **Day 1 of Each Phase** | |
| Laboratory | X | X* | Screening (or Day 1 predose in the lead-in phase if collected) for the lead-in phase; Day 1 predose for the injection phase |
| Vital Signs | X | X | Day 1 (Predose) for each phase |
| ECG | X | X | Screening (or Day 1 predose in the lead-in phase if collected) for all subjects |

* The results of the hematology with differential, and clinical chemistry tests on Day 1 are not required prior to administering the first oral dose of CAB 30 mg, but should be drawn prior to CAB administration.

## 5.3. Reporting Conventions

- Statistical data analyses will be performed by, or under the direct auspices of, Clinical Statistics and Programming, GlaxoSmithKline.

- Data will be listed and summarized according to GlaxoSmithKline reporting standards, where applicable. Listings will be sorted by Site, subject, phase, day, and time, noting treatment; summaries will be presented by treatment (for safety and study population) or sex (for PK data), or by Site (demog), day, and time.

- Unless stated otherwise, descriptive summaries will include n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and the between-subject CV (%CVb) for continuous variables, whereas n and percent will be used as summary statistics for categorical variables.

- Baseline or pre-dose assessment is the last available assessment prior to time of dose administration unless it is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables. Unscheduled assessments will be presented in listings.

- Deviations from planned times will be examined for scheduled assessments. PK parameters will be calculated using actual assessment times. Actual assessment times will be used in the individual concentration-time plots. Nominal times will be used for the purposes of summarization and in mean and median plots. Concentration-time data will be listed using actual assessment times.

- Any changes/deviations to the analyses specified in the RAP will be described in the final Clinical Pharmacology Study Report (CPSR).

- Version 9.4 or higher of the SAS system will be used to analyze the CRF data as well as to generate tables, figures, and listings. PK parameters will be calculated using standard non-compartmental methods using Phoenix WinNonLin Version 7 or higher.

- All final displays will be produced according to Clinical Data Interchange Standards Consortium (CDISC) reporting standards based on the final Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets.

## 5.4. Data Management

| Data Type | Source | Format of Data | Planned Date of Final File | Responsibility |
|---|---|---|---|---|
| Safety | Database | SDTM | DBF | Data Management |
| PK/Tissues samples | SMS2000 /PK HARP | DAT | Prior to SDL | DMPK |
| | SMS2000, Randomisation & CRF data (merge) | CSV file | Approximately 1 week after SDL | Data Management using EDU |
| | Derived PK parameters | CSV file | Approximately 4 weeks after DBF | CPMS |
| LAB | Local lab | SDTM | DBF | Data Management |

## 5.5. Premature Withdrawal and Missing Data

All subjects who withdraw prematurely from the study/study drug will be documented and the reason for their withdrawal recorded in the final Clinical Pharmacology Study Report (CPSR). All available data from subjects who withdraw will be listed and all available planned data will be included in the summaries according to the populations defined in Section 4.

In the event that the study is prematurely discontinued, all available data will be listed and a review carried out by the study team to assess which statistical analyses are still considered appropriate.

## 5.6. Derived and Transformed Data

### 5.6.1. Change from Baseline

The change from baseline will be calculated by subtracting the baseline values from the individual post-baseline values. If either the baseline or post-baseline value is missing, the change from baseline is set to missing as well.

### 5.6.2. Plasma, Tissues, Fluid Data

Plasma and a variety of compartment tissues and fluid samples are collected during the study, and all will be listed with actual time and calculated visit weeks. Samples with protocol deviation will be reviewed by the team to determine whether these samples will be excluded from the summary tables.

#### 5.6.2.1. Evaluable Concentrations and Parameters

Flags for evaluable concentrations for each type of samples will be created and are defined as samples collected within the specified window without major protocol deviations. Evaluable parameters are calculated based on evaluable concentrations.

Flags will be created for the samples which are collected when the injections are done at gluteal muscle under ultrasound guidance. Concentrations data could be summarized by gluteal muscle flag.

For the purposes of calculating summary statistics and for statistical analysis, only parameters with the exception of tmax will be $\log_e$ transformed.

Between subject's coefficient of variation (%CVb) will be calculated according to the following methods:

Untransformed Data : 100 * (SD/Mean)

Transformed Data : 100 * (sqrt(exp($SD_{log}^2$)-1))

where $SD_{log}$ indicates the standard deviation of log-transformed data.

### 5.6.3. Multiple Measurements at One Timepoint

Where multiple measurements are recorded for a particular time point, the mean of the measurements will be calculated and used in any derivation of summary statistics. However, all available data will be listed.

### 5.6.4. QTc interval

QTc interval will be corrected by both Bazett's (QTcB) and Fridericia's (QTcF) formula and will be included in all relevant listings.

QTcB interval (msec) = QT interval (msec) / square root (RR interval (msec)/1000)

QTcF interval (msec) = QT interval (msec) / cubic root (RR interval (msec)/1000)

If QTcB is provided by the Electrocardiogram (ECG) machine, then that RR value will be used to calculate the QTcF.

For example, if a vendor provides QTcB but not QTcF, RR will be calculated as:

RR = [(QT/QTcB)**2 ]*1000, provided at the SDTM level.

## 5.7. Assessment Windows

Scheduled visits and unscheduled visits for lab, ECG and vital sign data will be assigned to assessment windows by actual study day. For PK, tissues and fluid samples, actual days will be used to calculate the actual visit Week (round-up), and evaluable samples will be summarized by actual visit week. Actual days will be used for the listings, and scheduled windows will be used for the Summary Displays.

| Phase | Study Visit and Unscheduled Visit window | Reported on Summary Displays |
|---|---|---|
| Screen | 30 days prior to Day 1 | Screen |
| Oral Lead-in | Day 1, Day 14, Day 29 | Day 1, Day 14, Day 29 |
| Injection phase | Days 1,3,5,8 | Days 1,3,5,8 |
| | Week 4 ±3 days | Week 4 |
| | Week 8 ±3 days | Week 8 |
| | Week 12 ±3 days | Week 12 |
| | Week 24 ±3 days | Week 24 |
| | Week 36 ±3 days | Week 36 |
| | Week 52 ±3 days | Week 52 |

## 5.8. Values of Potential Clinical Importance

**ECG Values of Potential Clinical Importance (Healthy Volunteers)**

| ECG Parameter | Potential Clinical Importance Range (PCI) | Unit |
|---|---|---|
| Absolute QTc interval | >450 | msec |
| Increase from baseline QTc | >60 | msec |
| PR interval | <110 and >220 | msec |
| QRS interval | <75 and >110 | msec |

**Vital Sign Values of Potential Clinical Importance (Healthy Volunteers)**

| Parameter | Potential Clinical Importance Range (PCI) | Unit |
|---|---|---|
| Systolic Blood Pressure | < 85 and > 160 | mmHg |
| Diastolic Blood Pressure | < 45 and > 100 | mmHg |
| Heart Rate | < 40 and > 110 | bpm |

# 6. STUDY POPULATION

Study population data will be summarised by, or under the direct auspices of, Clinical Statistics, GlaxoSmithKline.

## 6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the screened and safety population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards if applicable. Details of the planned displays are presented in Section 11.1.1 and Section 11.1.4 of the RAP.

## 6.2. Subject Disposition

A summary table will be generated to provide the count of subjects included in each analysis population for the study (see Section 4 for definition of analysis populations) and this table will be displayed by treatment and overall.

The End of Study Record will be listed and summarized by Site and overall. The listing will include whether subjects prematurely withdrew from the study, the reason for premature discontinuation, along with the start and end date of investigational product (IP) dosing and the date of completion or premature discontinuation from the study.

## 6.3. Demographic and Baseline Characteristics

Demographic data includes date of birth, gender, race, and ethnicity. Demographic data will be summarized by Site and Overall, and listed for the Safety Population. Race will be summarized by Site and Overall, and listed separately from the other demographic characteristics.

Baseline characteristics (Height, weight, BMI, etc.) will be listed by subject and summarized by Site and Overall according to data display specifications given in Section 11.1.2 and Section 11.1.4.

## 6.4. Concomitant Medications

Concurrent medication verbatim text will be coded and classified by the Anatomical Therapeutic Chemical Classification level 1 (ATC Level 1) code and the preferred term using the GSK coding system, GSK DRUG. Subjects who take concurrent medications during the study will be summarized and listed according to data display specifications given in Section 11.1 of this RAP. Coding of concurrent medications will be the responsibility of the GSK coding group.

Information on whether or not the subject consented to having a pharmacogenetic sample drawn will be listed.

## 6.5. Treatment Compliance and Protocol Deviations

Information for each subject who did not receive the correct dose, the reason for not receiving the correct dose, and any other protocol deviations will be summarized by the important flag and by Site and listed by Site and subject. Subjects who did not satisfy all inclusion and exclusion criteria and corresponding criteria that were violated will be listed.

# 7. SAFETY ANALYSES

Safety data will be summarised descriptively and listed by according to GSK's Integrated Data Standards Library (IDSL) standards, or under the direct auspices of, Clinical Statistics, GlaxoSmithKline

No formal statistical analysis of the safety data will be conducted.

The precise format and content of Safety figures, tables and listings are shown in Section 11.1.2 and Section 11.1.4 of the RAP.

The tables will use the "Safety" population unless otherwise specified.

## 7.1. Extent of Exposure

A by-subject summary of treatments administered in each phase will be generated, with dose, number of doses and dosing start date and dosing end date. A by-subject listing of

data on subject exposure will be generated including dose date and time, unit, formulation, route, frequency and location.

## 7.2. Adverse Events

Adverse event verbatim text will be coded and classified by system organ class (body system) and preferred term using a standardized GSK coding system: Medical Dictionary for Regulatory Activities (MedDRA, v22 or higher). Treatment emergent AEs data and drug-related AEs for lead-in phase and for LA dosing phase will be summarized by Site and treatment and overall. The relationship of AE system organ class, preferred term, and verbatim text will be listed. All AEs will be listed by Site, subject and treatment. Serious adverse events (SAEs) will be listed. A listing of grade 3 or 4 non-ISR AEs will be provided if any grade 3 or 4 AE occur.

Injection site reaction (ISR) symptoms, size, severity grade and duration for the LA dosing phase will be summarized overall and will be listed by Site and subject.

For subjects who have an ISR that is serious, Grade 2 if persistent beyond 2 weeks, any Grade 3 or if any ISR persistent beyond 30 days and others if the Investigator or Medical Monitor feels it is medically necessary, a listing will be provided in table listing. All ISR data including treatment received and medical intervention as well as reaction outcome will be listed by subject. Plots of top 3 injection site reaction duration will be provided.

## 7.3. Deaths and Serious Adverse Events

Deaths and other serious adverse events will be listed if any of these events occur. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

A by-subject listing of AEs leading to withdrawal will be provided.

Patient profile for deep venous thrombosis/pulmonary embolus will be generated for cardiovascular event.

## 7.4. Pregnancies (as applicable)

If any female subjects become pregnant during the study, a narrative of such subjects will be provided.

## 7.5. Clinical Laboratory Evaluations

A listing of reference ranges for clinical laboratory tests performed during the study will be generated. Hematology, clinical chemistry and urinalysis (listing only) data will be listed by subject, phase, visit, and actual date and time and summarized by treatment and visit. Summary of change from baseline in hematology and clinical chemistry by treatment and visit will be created for each site. If any laboratory test results are outside of the reference range, they will be flagged with high/low and/or toxicity grade in the listing. Only the tests which have specified in the protocol will be included on the displays.

Laboratory abnormalities that are recorded as adverse events will be listed separately and corresponding lab values will be provided.

Modified Division of AIDS (DAIDS) AE grades will be derived in analysis dataset by using Division Of AIDS Table For Grading The Severity Of Adult And Pediatric Adverse Events Version 2.0, November 2014. Grades 2, 3, and 4 of lab abnormalities will be listed by Site, subject, phase, visit, treatment and actual date and time.

## 7.6. Other Safety Measures

Vital sign data (temperature, systolic and diastolic blood pressure, and pulse rate) will be summarized by treatment, visit, and planned time and listed by site, subject, phase, visit, planned time, and actual date and time. In addition, a listing of vital signs for subjects with abnormalities of potential clinical importance will be provided.

ECG data will be listed by site, subject, visit, and actual date and time. Clinically significant ECG abnormalities will be flagged.

Any surgical procedures will be listed.

Medical and medication history, physical examination, pregnancy and drug screen (including alcohol) results will be captured in the source document supporting the enrolment criteria and summary will not be provided.

MRI images and quantitative assessments will be collected and reported separately by GSK Platforms Technology Sciences. Only MRI collection dates will be provided in the listing package.

# 8. PHARMACOKINETIC ANALYSES

The reconciliation of the PK Case Report Form (CRF) and SMS2000 data will be performed by, or under the direct auspices of, Clinical Pharmacology Sciences and Study Operations (CPSSO), GlaxoSmithKline.

The merge of PK concentration data, randomisation and CRF data will be performed by, or under the direct auspices of, Clinical Statistics (Programmer), GlaxoSmithKline.

Derivation of pharmacokinetic parameters will be performed by, or under the direct auspices of, Clinical Pharmacokinetic Modelling Simulation (CPMS), GlaxoSmithKline.

Statistical analysis of pharmacokinetic parameters will be performed by, or under the direct auspices of, Clinical Statistics (Statistician), GlaxoSmithKline.

## 8.1. Reporting Standards for Pharmacokinetic

| | |
|---|---|
| **Pharmacokinetic Concentration Data** | |
| PC Windows Non-Linear (WNL) File | PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to GSK PK guidance<br>Note: Concentration values will be imputed as per GUI_51487 |
| Descriptive Summary Statistics, Graphical Displays and Listings | Refer to IDSL PK Display Standards.<br>Refer to IDSL Statistical Principle 6.06.1.<br>Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only. |
| **Pharmacokinetic Parameter Derivation** | |
| PK Parameter to be Derived by Programmer | The following PK parameters will be derived or extracted from SDTM PC file or SDTM PP by the Programmer:<br>From SDTM PC Concentrations:<br>Ctau on Day 29, C48h, C8d, CWk4, CWk8, CWk12, CWk24, CWk36, and CWk52 from concentration data (as data permit) & the ratios: VT:blood plasma, CT:blood plasma, CVF:blood plasma, CT:CVF, VT:CVF in women, and RT:blood plasma, RF:blood plasma and RT:RF in men and women (as data permit) at matched timepoints evaluated.<br>From SDTM PP file:<br>VT:blood plasma, CT:blood plasma, CVF:blood plasma, CT:CVF, VT:CVF in women, and RT:blood plasma, RF:blood plasma and RT:RF in men and women ratios for Cmax, AUC(0-∞), AUC(0-last), AUC(0-Wk4), AUC(0-Wk8) and AUC(0-Wk12) |
| **Pharmacokinetic Parameter Data** | |
| Is NQ impacted PK Parameters Rule Being Followed | Yes, refer to Standards for the Transfer and Reporting of PK Data using HARP. |
| Descriptive Summary Statistics, Graphical Displays and Listings | Refer to IDSL PK Display Standards & refer to Standards for the Transfer and Reporting of PK Data using HARP. |

## 8.2. Drug Concentration Measures

CAB concentrations will be collected at following time points after a single CAB 600 mg IM dose:

- Blood plasma (BP) of CAB concentrations: Day 1 (pre-dose, 4hr), Day 3 (C48h), Day 5 (C96h), Day 8 (C168h), Weeks 4, 8, 12, 24, 36, and 52 (CWk4, CWk8, CWk12, CWk24, CWk36 and CWk52)

- Cervical tissue (CV) and cervicovaginal fluid (CVF) of CAB concentrations in women: Day 3 (C48h), Day 8 (Cd8), Weeks 4, 8, and 12 (CWk4, CWk8, and CWk12)

- Rectal tissue (RT) and rectal fluid (RF) in men and women (as data permit): Day 3 (C48h), Day 8 (Cd8), Weeks 4, 8, and 12 (CWk4, CWk8, and CWk12)

- Vaginal tissue (VT) of CAB concentrations in women: Day 3 (C48h), and Week 8 (CWk8)

These concentrations will be determined directly from concentration-time data from each matrix (BP, CV, CVF, RT, RF, VT). Descriptive statistics (i.e. mean, standard deviation, median, minimum and maximum) and graphics will be created to describe the primary PK endpoints of interest.

Refer to the standard operating procedure, SOP-CPK-0001, for more information regarding the treatment of plasma concentrations below the assay's lower limit of quantification (BQL).

Individual concentration-time profiles and median/mean profiles from each matrix will be plotted. Each of the figures will contain one plot on the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. semi-log plot). See Section 11.1.3 Pharmacokinetic Figures and Tables for details.

## 8.3. Deriving and Summarizing Pharmacokinetic Parameters

Pharmacokinetic analyses will be the responsibility of the Clinical Pharmacokinetics Modeling & Simulation department within GlaxoSmithKline.

Plasma and tissue/fluid concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin 7 or higher (New Jersey). Pharmacokinetic parameters will be estimated via noncompartmental analysis using the linear up/log down application of the trapezoidal rule for model 200 (extravascular administration) of the WinNonlin program. Calculations will be based on the actual sampling times recorded during the study. The following CAB PK parameters will be calculated for each matrix if available:

- Cmax, tmax, AUC(0-∞), AUC(0-last), AUC(0-Wk4), AUC(0-Wk8) and AUC(0-Wk12) and t½ in blood plasma and in CT, and CVF in females and RT and RF in males and females.

1. CAB concentrations at Day 3 (C48h), Day 8 (Cd8), Weeks 4, 8, and 12 (CWk4, CWk8, and CWk12) in blood plasma and in CT, CVF in women, and in RT and RF in men and women (as data permit) will be considered as evaluable data if they are collected within 4 hours of schedule time for C48h and Cd8, and collected within ± 3 days of scheduled time for CWk4, CWk8 and CWk12. Actual weeks (rounding to the integer weeks) will be used for CWk24, CWk36 and CWk52.

2. VT samples will be considered as evaluable C48h and CWk8 concentration if samples are collected at Day 3 (C48h with 4hrs of window of scheduled collection), and Week 8 (CWk8 with ± 3 days of scheduled visit), in women following a single CAB 600 mg IM dose.

3. CAB concentration in VT, CT, CVF, RT, RF and BP on Day 29 will be considered as evaluable data if these samples are collected within 4hr of scheduled window.

4. The area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC(0-last)) will be determined using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations in blood plasma and in CT, and CVF in females and RT and RF in males and females.

5. The AUC extrapolated to infinity (AUC(0-∞)) will be calculated, where data permit, as the sum of AUC(0-t) and Ct/λz, where Ct is the observed plasma concentration obtained from the log-linear regression analysis of the last quantifiable time-point in blood plasma and in CT, and CVF in females and RT and RF in males and females.

6. AUC(0-Wk4), AUC(0-Wk8) and AUC(0-Wk12) are the area under the concentration time curve from time zero to week 4, week 8 and week 12 respectively, determined using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations in blood plasma and in CT, and CVF in females and RT and RF in males and females.

7. The first occurrence of the maximum observed plasma concentration (Cmax) will be determined directly from the raw concentration-time data in blood plasma and in CT, and CVF in females and RT and RF in males and females.

8. The time at which Cmax is observed (tmax), determined directly from the raw concentration-time data in blood plasma and in CT, and CVF in females and RT and RF in males and females.

9. The apparent terminal elimination half-life (t1/2) obtained as the ratio of ln2/ λz, where z is the terminal phase rate constant estimated by linear regression analysis of the log transformed concentration-time data in blood plasma and in CT, and CVF in females and RT and RF in males and females.

10. Ratios of time-matched AUC(0-∞), AUC(0-last), AUC(0-Wk4), AUC(0-Wk8) and AUC(0-Wk12) tissue matrices/luminal fluid: blood plasma (CVF:BP, CT:BP, RT:BP, and RF:BP), where data permit.

11. CVF:BP, CT:BP, VT:BP, CT:CVF, VT:CVF ratio in women and, RT:BP, and RT:RF ratios in males and females at matching time points (48h, 8d, 4w, 8w, 12w) where data permit during the injection phase, are calculated by CAB concentration in one of the matrices divided by another specified matrix. For example, the ratio of CVF, CT, VT, and RT concentration to blood plasma will be calculated as R_CVF (CT, VT, RT) = CVF (CT, VT, RT) concentration (ng/g) / Plasma Concentration (ng/mL). Assuming tissue density of 1g/mL, the tissue concentration to plasma ratio will be unitless. For CVF, CT, VT, and RT concentration below lower level of qualification (LLQ), it will be imputed as half of LLOQ.

Plasma PK parameters should be reported in μg/mL and μg•h/mLfor Cmax and AUC and in hours for tmax. Tissue concentrations in ng/g will be converted to ug/mL assuming a 1g/mL density and 1000ng/ug.

Clinical statistics and programming will extract the Ctau on Day 29, Day 3 (C48h), Day 8 (C8d), Weeks 4, 8, and 12 (CWk4, CWk8, and CWk12) from concentration data to calculate the ratios: CVF:BP, CT:BP, VT:BP, CT:CVF, VT:CVF ratio in women and, RT:BP, RF:BP and RT:RF ratios in males and females at matching time points where data permit during the injection phase.

## 8.4. Statistical Analyses

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of the statistics and programming, PAREXEL, under the direct auspices of statistics and programming, GlaxoSmithKline.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively by sex, by flag for evaluable data, by flag for injection location, by Site and overall. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

All the derived PK parameters will be listed and summarized by sex and overall. For each of these PK parameters, with the exception of tmax and ratios, the following descriptive summary statistics will be calculated for each treatment: n, arithmetic mean with associated 95% CI, standard deviation, median, minimum, maximum, geometric mean with associated 95% CI, standard deviation of logarithmically transformed data, and between-subject coefficient of variation (CVb(%)).

For tmax and all concentration ratios, no geometric mean, nor associated 95% CI or standard deviation of logarithmically transformed data will be provided.

A sex-based comparison will be made for all the evaluable blood plasma PK parameters and estimated ratio between female vs male and its associated 90% CI will be provided.

Log-transformed PK parameters (AUC(0-∞), AUC(0-last), AUC(0-Wk4)), AUC(0-Wk8), AUC(0-Wk12), Cmax and t½ in blood plasma) will be analyzed by analysis of covariance (ANCOVA). The analysis will consider sex as fixed effect with BMI as continuous covariate using the mixed linear models procedure within the SAS/STAT module of the SAS system (Version 9.4 or higher). For each log-transformed PK parameter, point estimate and its associated 90% CI will be constructed for the sex difference (females vs males), and the difference and its 90%CI will be exponentiated to obtain the ratio of geometric least-squares (GLS) means and its 90% CI on the original scale.

```
Examples of SAS codes:

Proc Mixed;
     class subjid sex;
     model logPKpar = sex bmi/ddfm=kr;
     lsmeans sex;
     estimate 'Females vs Males' Sex 1 -1 /cl alpha=0.1;
run;
```

Ratios will be calculated for each subject. Evaluable PK parameters and calculated ratios will be summarized by gender and/or overall for each matrix.

CAB concentration in each matrix from the oral lead-in phase may be compared with Weeks 4, 8, and 12 concentrations if data permit using the exploratory model below. Descriptive summary will be provided by sex, by flag for evaluable PK, by flag for injection location and/or overall.

```
Examples of SAS codes: if model converges

Proc Mixed; (only include Ctau from Day 29, Weeks 4, 8 and 12)
     class subjid sex visit;
     model log(Ctau) = sex bmi visit/ddfm=kr;
     random subjid;
     lsmeans sex;
     lsmeans visit;
     estimate 'Females vs Males' Sex 1 -1 /cl alpha=0.1;
     estimate 'IM vs oral' visit -1 0.3333 0.3333 0.3333/cl
alpha=0.1;
     estimate 'Week 4 vs week 12' visit 0 1 0 -1/cl alpha=0.1;
     estimate 'Week 8 vs week 12' visit 0 0 1 -1/cl alpha=0.1;
run;
```

Data display specifications for derived PK parameter summaries and listings are given in Section 11.1.3 of this RAP.

## 8.5. Relationship between Plasma CAB PK Concentration and Time Matched CVF, CT, VT, RT and RF CAB PK Concentration

The relationship between the plasma CAB PK concentration and the time matched CVF, CT, VT, RT and/or RF CAB PK concentration will be assessed with plots and by the SAS Proc Corr procedure.

# 9. REFERECE

GlaxoSmithKline Document Number 2014N213747_00: A Phase 1, Multicompartment Pharmacokinetic Study of Cabotegravir Long-acting in Healthy Adult Volunteers. Effective Date: 04-MAY-2015

GlaxoSmithKline Document Number 2014N213747_01: A Phase 1, Multicompartment Pharmacokinetic Study of Cabotegravir Long-acting in Healthy Adult Volunteers. Effective Date: 10-NOV-2015

GlaxoSmithKline Document Number 2014N213747_02: A Phase 1, Multicompartmental Pharmacokinetic Study of Cabotegravir Long-acting in Healthy Adult Volunteers. Effective Date: 30-MAR-2016

GlaxoSmithKline Document Number 2014N213747_03: A Phase 1, Multicompartmental Pharmacokinetic Study of Cabotegravir Long-acting in Healthy Adult Volunteers. Effective Date: 14-AUG-2017

# 10. ABBREVIATIONS & TRADE MARKS

## 10.1. Abbreviations

| Abbreviation | Description |
|---|---|
| ADaM | Analysis Data Model |
| AE | Adverse Event |
| ALT | alanine aminotransferase (SGPT) |
| ANCOVA | Analysis of Covariance |
| AST | Aspartate aminotransferase (SGOT) |
| ATC | Anatomical Therapeutic Chemical Classification level |
| AUC(0-last) | Area under the concentration time curve from time zero to last quantifiable time point |
| AUC(0-∞) | Area under the concentration time curve from time zero to infinity |
| AUC(0-Wk4) | Area under the concentration time curve from time zero to Week 4 |
| AUC(0-Wk8) | Area under the concentration time curve from time zero to Week 8 |
| AUC(0-Wk12) | Area under the concentration time curve from time zero to Week 12 |
| BMI | Body mass index |
| BP | Blood pressure |
| BPM | Beats per minute |
| BQL | Below the quantification limit |
| CAB | Cabotegravir |
| CDISC | Clinical Data Interchange Standards Consortium |
| CI | Confidence interval |
| Cmax | Maximum observed concentration |
| CPK | Creatine phosphokinase |
| CPMS | Clinical Pharmacokinetic Modelling Simulation |
| CPSSO | Clinical Pharmacology Sciences and Study Operations |
| $C\tau$ | Steady-state pre-dose CAB concentration |
| CT | Cervical tissue |
| CV | Coefficient of variance |
| CVb | Coefficient of variation between subjects |
| CVF | Cervicovaginal fluid |
| C48h | Concentrations observed at Day 3 (48h) |
| Cd8 | Concentration observed at Day 8 |
| CWk4 | Concentration observed at Week 4 |
| CWk8 | Concentration observed at Week 8 |
| CWk12 | Concentration observed at Week 12 |
| ECG | Electrocardiogram |
| GLS | Geometric least-squares |
| GSK | GlaxoSmithKline |
| HIV | Human immunodeficiency virus |
| IDSL | GSK's Integrated Data Standards Library |
| IM | Intramuscular(ly) |
| IP | Investigational product |
| ISR | Injection site reaction |

| Abbreviation | Description |
|---|---|
| LA | Long-acting |
| MRI | Magnetic resonance imaging |
| PK | Pharmacokinetic(s) |
| QTcB | QT duration corrected for heart rate by Bazett's formula |
| QTcF | QT duration corrected for heart rate by Fridericia's formula |
| RAP | Reporting and Analysis Plan |
| RF | Rectal fluid |
| RT | Rectal tissue |
| SAE | Serious adverse event(s) |
| SAS | Statistical Analysis Software |
| SD | Standard deviation |
| SDTM | Study Data Tabulation Model |
| SOP | Standard operating procedure |
| t½ | Apparent terminal phase half-life |
| VT | Vaginal tissue |

## 10.2. Trademarks

| Trademarks of ViiV Healthcare |
|---|
| None |

| Trademarks not owned by ViiV Healthcare |
|---|
| PAREXEL |
| SAS |
| Winonlin |

# 11. ATTACHMENTS

## 11.1. Table of Contents for Data Display Specifications

Listed below are the planned figures, tables and listings to be produced for inclusion in the clinical study report. Example shells from GSK1265744 studies LAI116815\final_cdisc, LAI114433\final, mid201741\final and GSK2881078\mid200030\final are located under the same compound (GSK1265744) in HARP. Example shells for some of the PK figures are also under the GSK2881078/mid200030 study reporting effort final.

Reporting Area

| | |
|---|---|
| HARP Server | : US1SALX00259 |
| HARP Area | : \ARPROD\GSK1265744\MID201767\Final_01 |
| QC Spreadsheet | : \ARWORK\ GSK1265744\MID201767\Final\Documents |

### 11.1.1. Study Population

| Table No. | Population | IDSL No. / Example Shell | Title | Additional Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 1.1 | Safety | LAI116815, Table 1.1 | Summary of Analysis Populations | By Site and Treatment and Overall | 3 | SAC |
| 1.2 | Safety | LAI116815, Table 1.2 | Summary of End of Study Record by Site and Overall | By Site and overall | 2 | SAC |
| 1.3 | Safety | LAI116815, Table 1.3 | Listing of End of Study Record | Include the sub-reason where it has. | 1 | SAC |
| 1.4 | Safety | IDSL, IE4 | Listing of Subjects with Inclusion/Exclusion Criteria Deviations | | 1 | SAC |
| 1.5 | Safety | LAI116815, Table 1.4 | Summary of Demographic Characteristics for Safety Population by Site | By Site and overall | 2 | SAC |
| 1.6 | Safety | IDSL, DM6 | Summary of Race for Safety Population | By Site and overall | 2 | SAC |
| 1.7 | Safety | IDSL, CP_CM4 | Summary of Concomitant Medications | Replace this listing with summary table by treatment if it has more than 4 pages of conmed data | 1 | SAC |
| 1.8 | Safety | IDSL, GN9 | Listing of Genetics Subject Accountability | With Site information | 1 | SAC |
| 1.9 | Safety | LAI116815, Table 1.8 | Listing of Treatment Non-Compliance by Site | Only list subjects with treatment non-compliance | 1 | SAC |
| 1.10 | Safety | LAI116815, Table 1.9 | Summary of Protocol Deviations | Sorted by Site | 1 | SAC |
| 1.11 | All Screened | mid201741, Table 1.11 | Summary of Screen Failure by Site | By Site | 2 | SAC |

## 11.1.2. Safety

### Figures

| Figure No. 2.X | Population | IDSL No. / Example Shell | Title | Additional Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 1 | Safety | LAI116815, Figure 2.3 | Individual Subject ISR Duration for the Top 3 ISRs | Select the top 3 ISRs, like Pain, nodule, and induration | 1 | SAC |

### Tables

| Table No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 2.1 | Safety | LAI116815/Table 2.1 | Summary of Exposure Data | Include number of dose(s), formulation/route, and injection site, needle length, fat depth, injection length, etc<br>Sorted by Site | 1 | SAC |
| 2.2 | Safety | IDSL, AE2 | Relationship of Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text | | 2 | SAC |
| 2.3 | Safety | IDSL, CP_AE1x | Summary of All Adverse Events | By Site and Overall | 2 | SAC |
| 2.4 | Safety | IDSL, CP_AE1x | Summary of Drug-Related Adverse Events | Include all study treatment related, not procedure related AEs<br>By Site and Overall | 2 | SAC |

| Table No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 2.5 | Safety | IDSL, CP_AE9a | Listing of Subjects with Serious Adverse Events | | 1 | SAC |
| 2.6 | Safety | IDSL, CP_AE9 | Listing of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study | | 1 | SAC |
| 2.7 | Safety | LAI116815, Table 2.7 | Listing of Grade 3 and 4 Adverse Events | | 1 | SAC |
| 2.8 | Safety | LAI116815, Table 2.8 | Summary of Injection Site Reaction by Site and Overall | This table summarizes the data at Subject level; 'LM CAB 600mg SD' only, by site and overall | 2 | SAC |
| 2.9 | Safety | LAI116815, Table 2.9 | Summary of ISR Event by Toxicity Grade for Each Site and Overall | This table summarizes the data at event level for 'IM CAB 600mg SD' only; by site and overall | 2 | SAC |
| 2.10 | Safety | LAI116815, Table 2.10 | Summary of Injection Site Reaction Symptoms Maximum Size Measured in Diameter(cm) by Site and Overall | Average the max of each event size for each subject with ISR by treatment; 'IM CAB 600mg SD' only | 2 | SAC |
| 2.11 | Safety | LAI116815, Table 2.11 | Summary of Duration of Injection Site Reaction by Site and Overall | This table summarizes the data at ISR event level; IM CAB 600mg SD' only | 2 | SAC |
| 2.12 | Safety | LAI116815, Table 2.12 | Listing of Grade 2 or Higher Injection Site Reaction Symptoms or ISR persist beyond 30 days | For ISR | 2 | SAC |
| 2.13 | Safety | LAI116815, Table 2.13<br>IDSL, LB13 | Listing of Reference Ranges for Clinical Laboratory Tests | | 1 | SAC |
| 2.14 | Safety | LAI116815, Table 2.14 | Summary of Hematology Data by Treatment and Time by Site and Overall | Include oral CAB 30mg and 600mg LA in one table | 2 | SAC |
| 2.15 | Safety | LAI116815, Table 2.15 | Summary of Change from Baseline in Hematology Data by Treatment and Time by Site and Overall | | 2 | SAC |

| Table No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 2.16 | Safety | LAI116815, Table 2.16 | Summary of Clinical Chemistry Data by Treatment and Time for Each Site and Overall | | 2 | SAC |
| 2.17 | Safety | LAI116815, Table 2.17 | Summary of Change from Baseline in Clinical Chemistry Data by Treatment and Time for Each Site and Overall | | 2 | |
| 2.18 | Safety | LAI116815, Table 2.19 | Summary of Treatment Emergent Grade 2 or Higher Lab Abnormalities for Each Site and Overall | Include all tests in which we have DAIDS criteria. | 1 | SAC |
| 2.19 | Safety | LAI116815, Table 2.20 | Listing of Treatment Emergent Grade 2 or Higher Lab Abnormalities | Include all tests in which we have DAIDS criteria. | 1 | SAC |
| 2.20 | Safety | LAI116815, Table 2.21 | Summary of Vital Signs by Treatment and Time | Include BP, HR, and Temperature | 2 | SAC |
| 2.21 | Safety | LAI116815, Table 2.22 | Summary of Change from baseline in Vital Signs by Treatment and Time | Include BP, HR, and Temperature | 2 | SAC |
| 2.22 | Safety | LAI116815, Table 2.23 | Listing of All Vital Signs for Subjects with Any Values of Potential Clinical Importance | | 1 | SAC |
| 2.23 | Safety | LAI116815, Table 2.24 | Summary of ECG Findings | | 2 | SAC |
| 2.24 | Safety | LAI116815, Table 2.25 | Summary of ECG Values | | 2 | SAC |
| 2.25 | Safety | LAI116815, Table 2.26 | Summary of Change from baseline for ECG Values | | 2 | SAC |
| 2.26 | Safety | LAI116815, Table 2.27 | Summary of Category of QTc Data by Treatment and Time | | 2 | SAC |
| 2.27 | Safety | LAI116815, Table 2.28 | Summary of Category of QTc Change from Baseline by Treatment and Time | | 2 | SAC |
| 2.28 | Safety | IDSL, CP_EG6 | Listing of Clinically Significant ECG Abnormalities | List all data for a subject with clinically significant abnormalities | 1 | SAC |
| 2.29 | Safety | IDSL, CP_EG4, LAI116815, Table 2.29 | Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance | | 1 | SAC |

| Table No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 2.30 | Safety | IDSL, SP1 | Listing of Surgical Procedures | See format | 1 | SAC |
| 2.31 | Safety | IDSL, MH2 | Listing of Medical Conditions | See format | 1 | SAC |

## 11.1.3. Pharmacokinetic Figures and Tables

Flag for injection location indicates whether the injection gets to the gluteal muscle, it is not necessary to be considered as not evaluable samples/parameters. Flag for evaluable sample/parameter indicates the samples are collected at specified window and injection location, and no major deviation of process. When specified by evaluable flag, by flag for injection location, it means the plots or tables should be generated for each flag levels only, and plus overall. When specified by evaluable flag and injection location, it means the plots or tables should be generated for each combination levels of evaluable and injection location, and plus overall. Footnote the treatments (oral CAB, or IM CAB) based on the sample collection days should be added when time (Days/Weeks) are presented in plots. Tissue/fluid data may contain up to 5 different matrices: vaginal tissue (VT), cervical tissue (CT), and cervicovaginal fluid (CVF) in healthy women and in rectal tissue (RT) and rectal fluid (RF) in healthy men and women (as data permit).

**Figures:**

| Figure No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 3.1 | PK Concentration | GSK1265744/LAI114433, Figure 11.1 | Individual Plasma Cabotegravir Concentration-Time Plots (Linear and Semi-Log) by Gender and Flag for Injection Location | Plot all data using actual schedule Days/Weeks, one symbol per gender and location (combinations), with multiple subjects on the same page, Footnote the treatment based on the sample collection days/Weeks | 1 | SAC |
| 3.2 | Evaluable Pharmacokinetic Plasma Parameter Summary Population | GSK1265744/LAI114433, Figure 11.2 | Mean Plasma Cabotegravir Concentration-Time Plots (Linear and Semi-Log) by Gender and Evaluable Flag and Overall | Four curves for gender by evaluable flag, all are on one page, one Overall, Footnote the treatment based on the sample collection days/Weeks | 1 | SAC |
| 3.3 | Evaluable Pharmacokinetic Plasma Parameter Summary Population | GSK1265744/LAI114433, Figure 11.3 | Median Plasma Cabotegravir Concentration-Time Plots (Linear and Semi-Log) by Gender and Evaluable Flag and Overall | Four curves for gender by evaluable flag, all are on one page, one Overall, Footnote the treatment based on the sample collection days/Weeks | 1 | SAC |

| Figure No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 3.4 | Evaluable Tissue_fluid and PK Parameter(IM) | GSK1265744/LAI114433, Figure 11.5 | Individual Tissue_fluid Cabotegravir Concentration-Time Plots (Linear and Semi-Log) by Evaluable Flag for Each Matrix | Include all subjects on the same page per matrix (VT/CT/CVF/RT/RF) with different symbol by Evaluable Flag, Footnote the treatment based on the sample collection days/Weeks Oral CAB: C24, IM CAB: Day 3 (C48h), Day 8 (Cd8), Week 4 (CWk4), Week 8 (CWk8), and Week 12 (CWk12) if available | 1 | SAC |
| 3.5 | Evaluable Tissue_fluid and PK Parameter(IM) | GSK1265744/LAI114433, Figure 11.6 | Mean Tissue_fluid Cabotegravir Concentration-Time Plots (Linear and Semi-Log) by Evaluable Flag and Overall for Each Matrix | Each matrix with a page and different symbol, by Evaluable Flag and Overall, Footnote the treatment based on the sample collection days/Weeks | 1 | SAC |
| 3.6 | Evaluable Tissue_fluid and PK Parameter(IM) | GSK1265744/LAI114433, Figure 11.7 | Median Tissue_fluid Cabotegravir Concentration-Time Plots (Linear and Semi-Log) by Evaluable Flag and Overall for Each Matrix | Each matrix with a page and different symbol by Evaluable Flag and Overall, Footnote the treatment based on the sample collection days/Weeks | 1 | SAC |
| 3.7 | Evaluable Tissue_fluid and PK Parameter(IM) | GSK2881078/mid200030 Figure 3.10 | Scatter Plot of Plasma Cabotegravir PK Concentration vs Time Matched Cabotegravir Concentration in Vaginal Tissue by Evaluable Flag | All Time-matched Concentrations, with a regression line and R from SAS Proc Corr procedure, for evaluable of Oral CAB: C24, and IM CAB data: Day 3 (C48h), Day 8 (Cd8), Week 4 (CWk4), Week 8 (CWk8), and Week 12 (CWk12) if available | 1 | SAC |

| Figure No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 3.8 | Evaluable Tissue_fluid and PK Parameter(IM) | GSK2881078/mid200030 Figure 3.10 | Scatter Plot of Plasma Cabotegravir PK Concentration vs Time Matched Cabotegravir Concentration in Cervical Tissue by Evaluable Flag | All Time-matched Concentrations, with a regression line and R from SAS Proc Corr procedure for evaluable of Oral CAB: C24, and IM CAB data: Day 3 (C48h), Day 8 (Cd8), Week 4 (CWk4), Week 8 (CWk8), and Week 12 (CWk12) if available | 1 | SAC |
| 3.9 | Evaluable Tissue_fluid and PK Parameter (IM) | GSK2881078/mid200030 Figure 3.10 | Scatter Plot of Plasma Cabotegravir PK Concentration vs Time Matched Cabotegravir Concentration in Cervicovaginal Fluid by Evaluable Flag | All Time-matched Concentrations, with a regression line and R from SAS Proc Corr procedure for evaluable of Oral CAB: C24, and IM CAB data: Day 3 (C48h), Day 8 (Cd8), Week 4 (CWk4), Week 8 (CWk8), and Week 12 (CWk12) if available | 1 | SAC |
| 3.10 | Evaluable Tissue_fluid and PK Parameter (IM) | GSK2881078/mid200030 Figure 3.10 | Scatter Plot of Plasma Cabotegravir PK Concentration vs Time Matched Cabotegravir Concentration in Rectal Tissue by Evaluable Flag | All Time-matched Concentrations, with a regression line and R from SAS Proc Corr procedure for evaluable of Oral CAB: C24, and IM CAB data: Day 3 (C48h), Day 8 (Cd8), Week 4 (CWk4), Week 8 (CWk8), and Week 12 (CWk12) if available | 1 | SAC |

| Figure No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 3.11 | Evaluable Tissue_fluid and PK Parameter (IM) | GSK2881078/mid200030 Figure 3.10 | Scatter Plot of Plasma Cabotegravir PK Concentration vs Time Matched Cabotegravir Concentration in Rectal Fluid, by Evaluable Flag | All Time-matched Concentrations, with a regression line and R from SAS Proc Corr procedure for evaluable of Oral CAB: C24, and IM CAB data: Day 3 (C48h), Day 8 (Cd8), Week 4 (CWk4), Week 8 (CWk8), and Week 12 (CWk12) if available | 1 | SAC |

## Tables

| Table No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 3.1 | Evaluable PK Plasma Parameter Summary | PKCT1 | Summary of Plasma Cabotegravir PK Concentration (unit)-Time Data by Gender, by Site, by Evaluable Flag and by Injection Location | Include the plasma CAB Concentration on Day 29 of oral lead-in and IM CAB Samples, do summary by Gender, by Evaluable Flag and by Injection location and overall | 2 | SAC |
| 3.2 | PK Parameter | GSK1265744/LAI114433 Table 11.3 | Listing of Derived Plasma Cabotegravir PK Parameters | Sort by clinical site, sex and subject ID with flags evaluable and injection location | 1 | SAC |
| 3.3 | Evaluable PK Plasma Parameter Summary | GSK1265744/LAI114433 Table 11.4 | Summary of Derived Plasma Cabotegravir PK Parameters by Gender by Site, by Evaluable Flag and by Injection Location | For each parameter, summarized the data by Gender, by Evaluable Flag, by Injection location and overall | 2 | SAC |
| 3.4 | Evaluable PK Plasma Parameter Summary | GSK1265744/LAI114433, Table 11.7 | Summary of Result of Plasma Cabotegravir PK Parameter Comparisons Between Gender for Evaluable PK | Limited to evaluable PK data, and include sex and BMI in model, evaluate the difference between gender for AUC(0-t), AUC(0-∞), Cmax, AUC(0-Wk4), AUC(0-Wk8), AUC(0-Wk12) and t1/2, | 3 | SAC |
| 3.5 | Evaluable PK Plasma Parameter Summary | GSK1265744/LAI114433, Table 11.7 | Summary of Result of Plasma Cabotegravir PK Parameter Ctau Comparisons Between Oral and IM for Evaluable PK | Limited to evaluable PK data, and include sex, BMI and Visits in model, evaluate the difference between IM vs oral CAB Ctau | 3 | SAC |
| 3.6 | Evaluable Tissue_fluid and PK Parameter(IM) | GSK1265744/LAI114433 Table 11.10 | Summary of Tissue and Fluid Cabotegravir Parameters for each Treatment and Matrix by Site, by Evaluable Flag and by Gender | Include the CAB Parameters from tissue/fluid on Day 29 of oral lead-in, put each by variable on different page or sub-category | 2 | SAC |
| 3.7 | Tissue fluid Parameter | GSK1265744/LAI114433 Table 11.8 | Listing of Derived Tissue and Fluid Cabotegravir Parameters | Sort by clinical site, sex and subject ID and flags for evaluable and injection locations | 1 | SAC |

| Table No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 3.8 | Evaluable Tissue_fluid and PK Parameter (IM) | GSK1265744/LAI114433 Table 11.10 | Summary of Tissue and Fluid to Blood Plasma Cabotegravir PK Parameter Ratio for each Matrix by Site and by Gender | Ratios of Tissue or fluid vs plasma for AUC(0-t), AUC(0-∞), Cmax, AUC(0-Wk4), AUC(0-Wk8), AUC(0-Wk12), for VT:blood plasma, CT:blood plasma, CVF:blood plasma, by site, by gender and overall | 2 | SAC |
| 3.9 | Evaluable Tissue_fluid and PK Parameter (IM) | GSK1265744/LAI114433 Table 11.10 | Summary of Tissue and Fluid to Blood Plasma Cabotegravir PK Concentration Ratios of Each Visit by Site and by Gender | Ratios of Tissue fluid vs plasma for oral C29d, and IM C3d, C8d, CWk4, CWk8, CWk12 of VT:blood plasma, CT:blood plasma, CVF:blood plasma, by site, by gender and overall | 2 | SAC |
| 3.10 | Evaluable Tissue_fluid and PK Parameter(IM) | GSK1265744/LAI114433 Table 11.10 | Summary of Tissue to Fluid Cabotegravir Parameter Ratios by Site and by Gender | Ratios of tissue vs fluid for AUC(0-t), AUC(0-∞), Cmax, AUC(0-Wk4), AUC(0-Wk8), AUC(0-Wk12), by site and by gender plus overall for ratios: CT:CVF, VT:CVF in women, and RT:RF in men and women (as data permit) | 2 | SAC |
| 3.11 | Evaluable Tissue_fluid and PK Parameter Population (IM) | GSK1265744/LAI114433 Table 11.10 | Summary of Tissue to Fluid Cabotegravir PK Concentration Ratios of Each Visit by Site, by Gender | Ratios of Tissue vs fluid for oral C29d, and IM C3d, C8d, CWk4, CWk8, CWk12 of for ratios: CT:CVF, VT:CVF in women, and RT:RF in men and women (as data permit) | 2 | SAC |
| 3.12 | Tissue fluid Parameter | GSK1265744/LAI114433 Table 11.8 | Listing of Individual Tissue and Fluid to Blood Plasma or Tissue vs Fluid Cabotegravir PK Concentration Ratios | Ratios of tissue fluid vs plasma or tissue vs fluid for oral C29d, and IM C3d, C8d, CWk4, CWk8, CWk12, include flags for evaluable data and injection location variables | 2 | SAC |

| Table No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 3.13 | Tissue fluid Parameter | GSK1265744/LAI114433 Table 11.8 | Listing of Individual Tissue and Fluid to Blood Plasma or Tissue vs Fluid Cabotegravir PK Parameter Ratios | Ratios of tissue fluid vs plasma or tissue vs fluid for AUC(0-t), AUC(0-∞), Cmax, AUC(0-Wk4), AUC(0-Wk8), AUC(0-Wk12), include flags for evaluable data and injection location variables | 2 | SAC |

### 11.1.4. ICH Listings

| Listing No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 1 | Safety | IDSL, DM4 | Listing of Demographic Characteristics | | 1 | SAC |
| 2 | Safety | IDSL, DM10 | Listing of Race | | 1 | SAC |
| 3 | Safety | IDSL, CP_AE9 | Listing of All Non-Injection Reaction Site Adverse Events | | 1 | SAC |
| 4 | Safety | IDSL, CP_AE9 | Listing of Injection Site Reactions | AE dataset | 1 | SAC |
| 5 | Safety | LAI116815, Listing 5 | Listing of All Injection Site Reaction Symptoms | ISR dataset | 1 | SAC |
| 6 | Safety | IDSL, CP_CM4 | Listing of Concomitant Medications | Provide listing if summary of Concomitant Medication table provided. | 1 | SAC |
| 7 | Safety | IDSL, CP_AE9 | Listing of All Adverse Events | AE severity is captured as “Maximum grade or intensity of event | 1 | SAC |

| Listing No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 8 | Safety | LAI116815, Listing 6 | Listing of Female Subjects or Female Partners of Male Subjects Who Became Pregnant During the Study | | 1 | SAC |
| 9 | Safety | LAI116815, Listing 7 | Listing of Hematology Data | | 1 | SAC |
| 10 | Safety | LAI116815, Listing 8 | Listing of Clinical Chemistry Data | | 1 | SAC |
| 11 | Safety | LAI116815, Listing 9 | Listing of Urinalysis Data | | 1 | |
| 12 | Safety | IDSL, CP_VS5 | Listing of Vital Signs | Include BP, HR, RR, Temperature | 1 | SAC |
| 13 | Safety | IDSL, CP_EG4 | Listing of ECG Values | | 1 | SAC |
| 14 | Safety | IDSL, CP_EG6 | Listing of Abnormal ECG Findings | | 1 | SAC |
| 15 | Safety | IDSL, CP_RA1x | Listing of Planned and Actual Treatments | | 1 | SAC |
| 16 | Safety | LAI114433, Table 10.1 | Listing of Exposure Data | Location of dose is applicable for LA only | 1 | SAC |
| 17 | Safety | LAI116815, Table 1.9 | Listing of Subject with Protocol Deviations | Sorted by Site | 1 | SAC |
| 18 | Safety | IDSL, CP_CM4 | Listing of Concomitant Medications | Replace this listing with summary table by treatment if it has more than 4 pages of conmed data | 1 | SAC |
| 19 | All Subjects Who Failed Screening | LAI117011, Listing 18 | Listing of Screen Failure | | 1 | SAC |
| 20 | PK Concentration | PKCL1x | Listing of Plasma Cabotegravir PK Concentration-Time Data | Include the flags for evaluable sample and injection location variables | 1 | SAC |
| 21 | Tissue_fluid Concentration | PKCL1x | Listing of Vaginal Tissue Cabotegravir PK Concentration-Time Data | Include the flags for evaluable sample and injection location variables | 1 | SAC |
| 22 | Tissue_fluid Concentration | PKCL1x | Listing of Cervical Tissue Cabotegravir PK Concentration-Time Data | Include the flags for evaluable sample and injection location variables | 1 | SAC |

| Listing No. | Population | IDSL No. / Example Shell | Title | Programming Notes | QC Level | Deliverable Priority |
|---|---|---|---|---|---|---|
| 23 | Tissue_fluid Concentration | PKCL1x | Listing of Cervicovaginal Fluid Cabotegravir PK Concentration-Time Data | Include the flags for evaluable sample and injection location variables | 1 | SAC |
| 24 | Tissue_fluid Concentration | PKCL1x | Listing of Rectal Tissue Cabotegravir PK Concentration-Time Data | Include the flags for evaluable sample and injection location variables | 1 | SAC |
| 25 | Tissue_fluid Concentration | PKCL1x | Listing of Rectal Fluid Cabotegravir PK Concentration-Time Data | Include the flags for evaluable sample and injection location variables | 1 | SAC |
| 26 | PK Parameter | SAS output | SAS Output of Summary of Result of Plasma Cabotegravir PK Parameter Comparisons by Gender | | 2 | SAC |
| 27 | PK Parameter | SAS output | SAS Output of Summary of Result of Plasma Cabotegravir PK Parameter Ctau Comparisons between IM and Oral CAB | | 2 | SAC |

Example SP1
Protocol: ABC123456 
Population: Intent-to-Treat/Safety/Other study specific

Listing X
Listing of Medical/Surgical Procedures

| Treatment | Inv. | Subject | Date of Procedure | Time of Procedure | Study Day | Classification | Condition |
|---|---|---|---|---|---|---|---|
| Trt A | PPD | PPD | PPD | 13:00 | -46 | Vascular Therapeutic Procedures | VARICOSE VEINS LIGATION |
| | | | PPD | | -15 | Head and Neck Therapeutic Procedures | OSSICULOPLASTY |
| | | PPD | PPD | | -39 | Head and Neck Therapeutic Procedures | EAR TUBE INSERTION |
| Trt B | PPD | PPD | PPD | 18:45 | -14 | Aortic Therapeutic Procedures | AORTIC BYPASS |

Example MH2
Protocol: ABC123456 
Population: Intent-to-Treat/Safety/Other study specific

Listing X
Listing of Medical Conditions

| Treatment | Inv. | Subject | Classification | Condition | Status |
|---|---|---|---|---|---|
| Treatment A | PPD | PPD | Hepatobiliary | HEPATITIS A | Current |
| | | | Psychiatric | PARANOIA COMBINED WITH MANIA. | Past |
| | | PPD | Eye | ASTIGMATISM | Current |
| Treatment B | PPD | PPD | Metabolism and nutrition | RICKETS | Current |